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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,870	04/18/2002	Hee-Yong Lee	5333-02600	8319

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Eric B Meyertons
Conley, Rose, & Tayon, P.C.
P O Box 398
Austin, TX 78767

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,870	LEE ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,9-11,13-15 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,9-11,13-15 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment and remarks dated 4-7-05 is acknowledged.

Claims 1, 5, 9-11, 13-15 and 19-21 are pending.

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

Claims 1, 5, 9, 13-15, 19-29, 31, 32 and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,470,582 to Supersaxo et al (Supersaxo in view of US 4,046,750 to Rembaum OR Supersaxo in view US 6,326,021 to Schwendeman (Schwendeman).

Supersaxo et al. teaches a controlled release pharmaceutical composition comprising a physiologically active agent dispersed in preformed porous polymeric microparticles. The active agent concentration may be up to about 10% by weight to achieve controlled release. Each of the porous microparticles has a plurality of preformed pores into which active agent is loaded and from which the active agent is subsequently released to the environment of use. The compositions are capable of delivering physiologically effective amounts of active agent for at least 30 days. See abstract. The microparticles are polymer of polylactic, polyglycolic, or copolylactic/glycolic) acid and the active agent is a polypeptide. In a process for preparing the pharmaceutical compositions, the preformed porous microparticles are suspended in a solution of the active agent. After the active agent has deposited on the

microparticles, they are dried, and further processed as required to remain a stable, biologically active pharmaceutical composition. See col. 2, lines 4-34. After adding the active agent, the microparticles may be dried by freeze-drying. See col. 5, lines 40-43. The release rate may be controlled by co-incorporation of release rate modifying excipients and additives. Additionally, Supersaxo teaches that in the event the active agent is one that is deactivated by freeze-drying, a cryoprotectant may be added. Suitable excipients, additives, and cryoprotectants include proteins, such as serum albumin; carbohydrates, including simple sugars such as mannitol and sucrose and polysaccharides such as dextran, lipids and surfactants such as polysorbate 80, see page 4, lines 40-54. The microparticles, which may assume a variety of shapes, generally have diameters of from about 50 to about 400 microns and are extensively permeated with a network of pores into which the active agent is introduced. The active agent containing microparticle can be easily administered in various dosage forms. For example, an injectable formulation of the microparticles may be dispersed in a suitable aqueous medium, optionally containing preservatives (e.g. methylparaben) and/or isotonizing agents (e.g. sodium chloride, sorbitol). The dose of the controlled release composition and the selection of suitable adjuvants, carriers, and solvents will depend upon the nature and amount of physiologically active agent in the microparticles, the dosage form, the desired duration of release, the recipient animal and purpose of the administration. Supersaxo does not disclose the microparticles having accessible ionic functional groups.

Supersaxo fails to teach biodegradable polymer with cationic functional groups.

Rembaum teaches binding of polyquaternary cationic polymeric segments to biocompatible porous particles containing halide or ternary amine sites forming modified beads. The beads offer a large positively charged surface area capable of binding polyanions such as heparin, DNA or bile salts or monoanions such as penicillin, pesticides etc., for slow release from the suspension and thus have a utility in clinical, diagnostic or analytical applications (col. 2). Rembaum teaches that the presence of hydroxyl, carboxy or amine groups on the microsphere beads permit covalent bonding of biomolecules such as haptens, enzymes, antibodies or lectins to the beads and the biomolecules bound can be used for diagnosis or treatment of a diseased condition. Examples 7-13 of Rembaum teach the preparation of microspheres containing aminofunctional groups.

Schwendeman teaches a method of making biocompatible base polymer particles that have functional groups attached on their surfaces. The process of preparing biocompatible polymer particles involves attaching a surface-active polymer on the base polymer such that the hydrophilic functional groups of the former demobilize the base polymer. The base polymers of Schwendeman may be selected from biocompatible, biodegradable or bioresorbable polymers (col. 2,m lines 56-col. 3, lines 14), and the surface active polymer (SAFP) comprises a polymeric backbone with functional groups such as amines, hydroxyl, carboxylic, thiol etc., that are covalently bonded. Examples of SAFP include polylysine, polyglutamic acid etc (col. 3, lines 15-45). Schwendeman teaches preparing microspheres by solvent evaporation method and the resulting particles are in the same size range as claimed (col. 4, lines 1-30 and

col. 4, lines 43-col. 5, lines 9). Schwendeman further teaches incorporating a drug by adding into the polymer particle, where the bioactive molecules may be attached to the SAFP (col. 4, lines 37-43).

It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to add polymers or polymeric segments carrying cationic groups such as quaternary groups (Rembaum) or amines (Schwendeman) to the biocompatible or biodegradable polymers of Supersaxo so as to functionalized or add functional groups to the polymers, during the preparation of polymeric microspheres because Rembaum teaches that cationic modified microspheres are stable, do not coalesce in suspension, readily bind anionic molecules such DNA, RNA, heparin etc., penetrate quickly into living cells and allows covalent binding of biomolecules such as vitamins, enzymes to the polymers and hence are useful in diagnostic as well as therapeutic applications. Further, Schwendeman also suggests that attaching functional groups on the polymer during the microsphere formation enables targeting of the biomolecules to a particular tissue without altering the bulk properties of the polymer itself and yet achieve a slow release of the drug or biomolecules. Accordingly, a skilled artisan would have been motivated to modify the surface of the polymers of Supersaxo by adding cationic groups such as amines or quaternary amines with an expectation to improve the incorporation of biomolecules into the microspheres and thus their tissue targeting as well as a slow and sustained release. Further, optimizing the amount of the drug to be incorporated, pH by adding an acidifying or an alkalizing agent, without affecting the ability to

functionalized or attach the desired functional groups (cationic or anionic) to the polymer by routine experimentation would have been within the scope of a skilled artisan.

Claims 1, 10, 11, 21, 29-30, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,470,582 to Supersaxo et al (Supersaxo) in view of Mady et al.

Supersaxo fails to teach the claimed surfactants. Mady studied effect of addition of surfactants to microsphere and observed that surfactants influence the nature of microsphere, structure, mecahnism of drug entrappment and release Mady teaches preparing Eudragit microspheres emoloying solvent evaporating technique. The microspheres of Mady contain an acidic drug ibuprofen and the surfactants cetrimide (cationic) or dioctyl sodium sulfosuccinate (DOSS, anionic) as anti-aggregating agents, in acidic aqueous phase. Mady teaches that the amount of initial drug released increased with an increase in the concentration of cetrimide and that the release pattern of the drug was smooth with 0.5% DOSS. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to chose cationic surfactants such as cetrimide or anionic surfactants such as DOSS in the preparation of microspheres of Supersaxo because Mady suggests that the drug entrappment and release pattern are increased with the above surfactants. Thu, askilled artisan would have expected an increase in the drug loading and a smooth relelase of the drugs incorporated in the microspheres.

Response to Arguments

Applicant's arguments filed 4-7-05 have been fully considered but they are not persuasive.

Supersaxo in view of Rembaum:

Applicants admit that Supersaxo appears to teach porous biodegradable polymers but argue that Rembaum does not teach biodegradable polymers and instead teaches formation of polyacrylate polymers polymer. Applicant further submits that adding the monomers of Rembaum to the monomers of Supersaxo would not appear to produce a biodegradable polymer. Applicant submits that the Office Action does not provide sufficient support for the assertion that the combination of Supersaxo and Rembaum would render obvious the features of Applicant's claims because adding a monomer that produces a polymer that is not biodegradable to a monomer that produces a biodegradable polymer would not be an obvious procedure if the desired result were to produce a biodegradable polymer.

Applicants arguments are not found persuasive because Rembaum teaches that the addition of polyquaternary cationic segments to the polymeric particles render the polymeric microparticles stable and also afford the latter the ability to bind anionic active agents such as heparin, DNA etc., due to the polycationic surface charge imparted by the cationic segments. Accordingly, one of an ordinary skill in the art would have been motivate to modify the micropsheres of Supersaxo by adding a cationic group with an expectation to bind anionic active agents and also impart stability. A careful review of

the instant application reveals that applicants desire an increased incorporation of the active agent into porous microspheres due to ionic functional groups, which is the same advantage taught byRembaum. Accordingly, the argument that the polymers of rembaum are not biodegradable is moot. The secondary reference has not been cited to add the polymers (non-biodegradable polymers) of Rembaum to the composition of Supersaxo and instead, to show that the teachings of Rembaum provide the motivation to introduce ionic groups into porous microparticles particles.

Applicants argue that Rembaum does not appear to teach or describe the binding of peptides or proteins, having a low molecular weight, such as penicillin, pesticides, sex attractants, etc may be formed and thus used in a slow release formulation. Therefore, it is argued it would appear that for polyanions, such as peptides and proteins would bind to the polymers of Rembaum irreversibly. The combination of irreversible binding and non-degradable polymers would not be suited for a sustained release composition. Applicants' arguments are not persuasive because it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Instant claims are not limited to any particular active agent not to any specific relelase rate. The claims in the instant also fail to recite the specific binding of the active agent in a reversible or irreversible fashion.

Supersaxo in view of Schwendeman et al:

Applicants admit that Supersaxo teaches porous micropsheres. Applicants argue that Schwendeman appears to teach formation of a mixed polymer that includes one or more functional groups capable of forming covalent lirtkages with a bioactive molecule. Applicants recite the portions of Schwendeman (col. 3, lines 33-40) and argue that contrary to the teachings of Schwendeman, Applicant's claims are directed to encapsulating a biopharmaceutical compound by using ionic interactions between the compound and the particle and argue that the combination of Supersaxo and Schwendeman does not appear to teach or suggest all of the features of Applicant's claims. Applicants arguments are not persuasive because Schwendenman states (in the above refered col. 1, lines 16-44), that injectable microsphere preparation whereinthe covalently linking conjugatable or ligatable groups to the polymer, with particular empahsis on peptide vaccines, is not advantageous, thus teaching away from covalent linking. Schwendenmann teaches modifying the surface of biodegradable polymer (by attaching a surface active material), for a sloww and efficient release of active agent. Further, with respect to the caovalent linking of the reference (col. 3, lines 33-40), cited by applicants, the covelent linking described by the reference is clearly of the SAFP with the base polymer and not with the active agent to be released. Further, examiner that the process of preparation of the polymer taught by the reference involves the same steps as that of the instant examples (col. 4). Accordingly, absent showing evidence to the contrary, the active agents in the teachings of Schwendenman bind with the ionic groups of SAFP and not by covalent modification.

Supersaxo in view of Mady:

Applicant submits that the cited art does not appear to teach or suggest at least the quoted features of claims 1 and 21 because Mady does not appear to teach or suggest the use of biodegradable polymers and instead is directed to the formation of Eudragit polymers which are polyacrylate polymers. For at least the same reasons recited above with respect to the Rembaum reference, Applicant submits that the combination of Supersaxo and Mady does not appear to teach or suggest all of the feamres of Applicant's claims. Applicants arguments are not persuasive because as also explained (with reference to Rembaum), the secondary reference has not been cited to add the polymers (non-biodegradable polymers) of Mady to the composition of Supersaxo and instead, to show that the teachings of Mady provide the motivation to add the calimed surfactants in the preparation of microspheres, so as to achieve increased drug loading and smooth release of drugs.

Applicants argue that Mady appears to teach that the surfactant is not intended to be incorporated into the microsphere, rather it is intended to inhibit aggregation during the preparation of the microspheres. Additionally, Applicant notes that when preparing microspheres using a solvent evaporation method the added surfactant is only added to the aqueous phase. Applicants argument that Mady's use of a surfactant is for a different purpose than Applicant's claimed use is not persuasive because, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd.

Pat. App. & Inter. 1985). In the instant case, the claimed steps do not recite the phase to which the surfactant is added and accordingly does not distinguish from the teachings of Mady. F with respect to the arguement that the article describes the use of centrimide, a cationic surfactant, and DOSS an anionic surfactant, both of which were used in the encapsulation of an acidic medicine, ibuprofen, examiner notes that instant claims do not exclude the presence of other surfactants along with cationic surfactants, nor do the claims recite any ratio of encapsulation. Accordingly, the arguments are not persuasive.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lakshmi S Channavajjala
Examiner
Art Unit 1615
June 17, 2005

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600